

REMARKS

Claims 1-15 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order in which they appear in the prior Office Action.

1. Withdrawal of Rejections Under 35 U.S.C. §112, Second Paragraph and 35 U.S.C. §102(b)

Applicants acknowledge with appreciation the withdrawal of the rejection of claims 14-15 under 35 U.S.C. §112, second paragraph. Applicants also acknowledge with appreciation the withdrawal of the rejection of claims 1-7 and 9-15 under 35 U.S.C. §102(b).

2-3. Rejection of Claims 1-15 Under 35 U.S.C. §103(a) Over Winkler et al. in View of Goldberg et al.

Claims 1-15 stand rejected as allegedly obvious over Winkler *et al.* (US 5,885,837) in view of Goldberg *et al.* (US 5,959,098). The Examiner has acknowledged that Winkler *et al.* does not teach a vertical substrate position. The Examiner asserts that “Goldberg et al teach the similar method wherein the surface is maintained in a vertical position during synthesis thereby facilitating removal of bubbles from the cavity which from [sic] during the synthesis process.” The Examiner further alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the vertical positioning of Goldberg *et al.* to the synthesis of Winkler *et al.* “for the expected benefit of facilitating bubble removal as taught by Goldberg et al.”

Applicants respectfully traverse the rejection. MPEP §2142 states:

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully believe that there is no motivation or suggestion for one of ordinary skill in the art to combine the method of Winkler *et al.* with the vertical flow cell positioning of Goldberg *et al.* First, Winkler *et al.* does not teach that bubble formation is problematic in its disclosed method of array preparation. One of ordinary skill in the art would not have identified bubble removal as a problem to be solved and thus would have had no motivation to look to Goldberg *et al.* for a solution to the problem. While Applicants do not concede that the method of Winkler *et al.* can necessarily be modified as taught by Goldberg *et al.*, even if modification were technically possible, “the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.” See *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q 1125, 1127 (Fed. Cir 1984).

Moreover, Applicants respectfully assert that a closer reading of Goldberg *et al.* reveals that the reference actually teaches that the positioning of the inlet and outlet at opposite ends of the panel is the suggested solution to the regulation of bubble formation rather than vertical positioning of the flow cell. Goldberg *et al.* states, “As shown, inlet and outlet ports 306 and 307, respectively, are located at opposite ends of the panel. This configuration improves fluid circulation and regulation of bubble formation in the cavity.” (col. 16, lines 13-16). The reference goes on to teach that if the flow cell is mounted vertically, then the outlet and inlet are located at the top and bottom ends of the cavity, respectively, but the reference does not teach or suggest that vertical positioning of the flow cell *in and of itself* improves fluid circulation and regulates bubble formation. Thus, even if one of ordinary skill in the art were to consider modifying the method of Winkler *et al.* to facilitate bubble removal as suggested by Goldberg *et al.*, the appropriate modification would consist of positioning of inlet and outlet at opposite ends of the substrate as explicitly taught by Goldberg *et al.* rather than vertically positioning the substrate as suggested by the Examiner. Thus, even if the combination of the reference teachings were made, there would have been no reasonable expectation of success for the claimed invention founded in the prior art.

Accordingly, it is Applicants’ position that the claimed invention is not *prima facie* obvious over Winkler *et al.* in view of Goldberg *et al.* Applicants respectfully request reconsideration and withdrawal of the rejection.

4. Rejection of Claims 1-15 Under 35 U.S.C. §103(a) Over Gamble et al. in View of Winkler et al.

Claims 1-15 stand rejected as allegedly obvious over Gamble *et al.* (US 5,981,733) in view of Winkler *et al.* (US 5,677,195). The Examiner states that Gamble *et al.* teaches a method for nucleic acid array synthesis wherein the support has a different position relative to the support in the prior attaching step (i.e., moved along the X-Y axis, Column 12, lines 52-54) but *does not* teach the rotational position is different from that in a previous attachment/binding step. The Examiner further states that Winkler *et al.* describes a method for nucleic acid array synthesis wherein the support is rotated prior to, coincident with, or subsequent to either binding or attaching steps and wherein the support has a *different* rotational position relative to a previous step (Column, 15, lines 53-67). The Examiner maintains that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify Gamble *et al.* to provide a different rotational position relative to the previous attachment/binding step as taught by Winkler *et al.* “for the expected benefit of producing different flow patterns across the substrate as desired by Winkler et al.”

The Examiner states that Applicants’ prior arguments are unpersuasive because Applicants have allegedly provided no evidence supporting their assertions. Applicants note that the Examiner cites *In re Schulze* and MPEP §716.01(c) in support of the position that arguments of counsel cannot take the place of evidence in the record. However, Applicants respectfully submit that the present situation is not one identified in MPEP §716.01(c) as requiring an affidavit or declaration, and moreover, that adequate evidence of Applicants’ position is provided by the cited references themselves as discussed in more detail below.

Applicants respectfully traverse the rejection and again note that in order to establish a *prima facie* case of obviousness there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants respectfully assert that there is no *prima facie* case of obviousness based on the cited art because there is no motivation or suggestion to modify the

method of Gamble *et al.* to alter the rotational position relative to the previous attachment/binding step as disclosed by Winkler *et al.*

In particular, Gamble *et al.* does not disclose that there is a need for or benefit in producing different flow patterns across the substrate. In fact, Gamble *et al.* *does not even comment on flow channels or flow patterns*, suggesting that the production of different flow channels or patterns is not relevant to the disclosed methods. In fact, Gamble *et al.* teaches a method in which virtually the entire surface of the substrate is coated with reagent in each attaching step; thus, flow patterns are not relevant to the methods disclosed by Gamble *et al.*

In commenting on Applicants' arguments in the reply to the Office Action of March 1, 2004, the Examiner has alleged that "the principle of operation of both Gamble and Winkler is the synthesis of molecular arrays." Applicants respectfully submit that this is overly broad. While both Gamble *et al.* and Winkler *et al.* disclose methods for the synthesis of molecular arrays, the principles of operation of the respective methods, that is, the scientific concepts that are successfully exploited in their design, are different. The Examiner has correctly noted that Gamble *et al.* teaches "the method wherein the support is held in a vertical position for reagent delivery (column, 4, lines 21-34) whereby the *entire surface* of the substrate is coated with the reagent" (emphasis added). This is in stark contrast to the method of Winkler *et al.* wherein a "series of channels or grooves are formed on or adjacent a substrate" and where "reagents are *selectively* flowed through or placed *in the channels or grooves...*" (column 2, lines 1-3). One of ordinary skill in the art would readily appreciate that a method for the synthesis of arrays in which the *entire* substrate is coated with reagents is different in its principle of operation from one in which the reagents are *selectively* flowed through or placed in channels. Applicants assert that this difference in principle of operation between Gamble and Winkler is fully supported by their respective disclosures and requires no additional evidence.

As such, one of ordinary skill in the art would have had no motivation to combine the methods of Gamble *et al.* and Winkler *et al.* Gamble *et al.* does not disclose that different flow patterns would be an advantage and/or improvement or that they can even be successfully applied to the invention disclosed therein. The prior art must suggest the desirability of the modification (see *In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q 1125, 1127 (Fed. Cir 1984),

which it clearly does not. In particular, one of ordinary skill in the art would have perceived no benefit to utilizing the substrate rotation step disclosed by Winkler *et al.* in the method of Gamble *et al.* because there would have been no expected benefit to producing different flow patterns across the substrate in view of the fact that the entire substrate is contacted with reagent in the method of Gamble *et al.*

In addition, assuming, *arguendo*, that one were to rotate the substrate of Gamble *et al.* such that the substrate had a different rotational position as compared with the prior attaching step, Applicants respectfully submit that the device and method disclosed by Gamble *et al.* would be unsuited for its intended purpose. Applicants respectfully highlight that Gamble *et al.* discloses an invention which is mechanical in certain aspects, such as substrate positioning. The sequence of movements of this machine are clearly disclosed in Figures 7A-C and in the text (column 7, line 50 to column 8, line 15). Specifically, the rotational positioning of the support/substrate in Gamble *et al.* is the same during each of the nucleotide addition steps. Figure 7 shows that in moving from the jetting device to the reaction chamber, the support is first rotated from horizontal to a vertical orientation, and then is rotated such that the longer dimension of the support is oriented along the z-axis. The support is then returned to the exact same position for each of the nucleotide addition steps, despite the rotation between nucleotide addition steps. During this sequence of motions, the substrate 20 interfaces or mates with the reaction chamber cell 29 (Figure 7). The reaction chamber cell 29 is clearly shown not to rotate, nor is it suggested to rotate. If the substrate 20 were to attain a different rotational position relative to a previous attachment step (90 degrees, for example in Figure 7C) it would not mate with the reaction chamber cell 29 (which does not rotate). Support for this assertion is evident, especially to one of ordinary skill in the art, from the Gamble *et al.* disclosure, Figure 7 in particular. The support must interface in a specific manner with the reaction chamber such that “the majority of the surface of the substrate in the reaction chamber cell is between the path of the reagent stream from the bottom port to the top port” (Column 7, lines 3-6). This specific interface would not be possible if the substrate were to attain a different rotational position relative to a previous attachment step as in the method of Winkler *et al.* This is apparent, especially to one of ordinary skill in the art, from inspection of Figure 7 of Gamble *et al.* Deviation from the set substrate position would result in the inability to form a “sealed, environmentally controlled enclosure” within the reaction chamber, this latter being disclosed by

Gamble *et al.* as important for synthesis of oligonucleotides using phosphoramidites (Column 3, lines 51-55 and Column 12, lines 21-26). Again, inspection of Figure 7 reveals that if the substrate were to attain a different rotational position relative to a previous attachment step as in the method of Winkler *et al.*, the interface between the substrate **20** and the reaction chamber **29** would not match and would not be “sealed.” One of skill in the art would not have a reasonable expectation of success in modifying the method of Gamble *et al.* as disclosed by Winkler *et al.* in light of the likely inability of the substrate **20** and the reaction chamber **29** to interface properly.

Applicants respectfully submit that no additional evidence of the above statements is required, as the disclosure of Gamble *et al.* and the knowledge of one of ordinary skill in the art are sufficient to arrive at this conclusion. Modification of the method of Gamble *et al.* such that the substrate attains a different rotational position relative to a previous attachment step would require reconstruction and or redesign of the Gamble device, such as accommodation of rotation of the reaction chamber **29**. Case law has shown that such a redesign is evidence for non-obviousness (see *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CPPA 1959), 270 F.2d at 813, 123 USPQ at 352).

Applicants respectfully assert that there would have been no proper motivation for one of ordinary skill in the art to combine the teachings of Gamble *et al.* with those of Winkler *et al.* Applicants also maintain that in view of the design limitations of the Gamble device, there would have been no reasonable expectation of success in combining the teachings of Gamble *et al.* with those of Winkler *et al.* In view of the above arguments, Applicants believe that the instant invention is not rendered obvious by Gamble *et al.* in view of Winkler *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7725. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

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Respectfully submitted,

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